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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/120,970	07/22/98	CURTISS R	MEGAN-100CON

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EXAMINER	
PORTNER, V	
ART UNIT	PAPER NUMBER
1645	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic...(s)
09/120,970	Curtiss

Examiner	Art Unit
Portner	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 12, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *30-33, 35-39, and 41-76* is/are pending in the application.

4a) Of the above, claim(s) *66-76* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *30-33, 35-39, and 41-65* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *30-33, 35-39, and 41-76* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim 40 has been canceled.

Claims 30-33,35- 39, 41-65, and 66-76 (new claims) are pending.

Election/Restriction

1. Newly submitted claims 66-74 are directed to an invention that is independent or distinct from the invention originally examined for the following reasons: The host cells of new claims 66-76 comprise:

a. Two copies of the essential gene, the native gene and a copy of the native gene; both genes are functional; and

b. The presence of a lethal gene is not recited in the independent claim.

The newly submitted claims recite claim limitations drawn to a genus of host cells that have not been previously examined. Claim 30 previous recited host cells that comprise at least one essential gene or one lethal gene. Claim 66 does not recite the presence of a lethal gene.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 66-74 stand withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections Withdrawn

2. Claim 61 rejected under 35 U.S.C. § 112, first paragraph, deposit requirement in view of the arguments presented in paper number 13, submitted March 6, 2001.

3. Claim 51 rejected under 35 U.S.C. § 112, second paragraph, in view the phrase "and promoter elsewhere in the cell" no longer being recited in the claim.

4. The double patenting rejection is withdrawn.

Rejections Maintained

5. Claims 30-33 and ~~35-64~~ 35-39,41-64 rejected under 35 U.S.C. 112, first paragraph, scope is maintained for reasons of record in paper number 12, paragraph 5.

6. Claims 30-33 and ~~35-64~~ 35-39, 41-64 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 12, paragraph 7.

7. Claims 30-33,35-38,48-49 and 65 rejected under 35 U.S.C. 102(b) as being anticipated by Nakayama et al (1988) **or** Curtiss et al (1989)for reasons of record in paper number 12, paragraph 10.

8. Claims 30-33,35-38, 48-49 and 65 rejected under 35 U.S.C. 102(e) as being anticipated by Curtiss, III (US Pat. 5,672,345) for reasons of record in paper number 12, paragraph 11.

9. Claims 30-33,35-38 and 65 rejected under 35 U.S.C. 102(b) as being anticipated by Jagusztyn-Krynicka et al (1993) for reasons of record in paper number 12, paragraph 12.

10. Claims 30-33,35-38 and 65 rejected under 35 U.S.C. 102(b) as being anticipated by Gentry-Weeks et al (1992) for reasons of record in paper number 12, paragraph 13.

11. Claims 30-33,35-38 and 65 rejected under 35 U.S.C. 102(b) as being anticipated by Schodel et al (Infection Immunity, May 1994)for reasons of record in paper number 12, paragraph 14.

12. Claims 30-33,35-38 and 65 rejected under 35 U.S.C. 102(b) as being anticipated by Cieslak et al (1993)for reasons of record in paper number 12, paragraph 15.

13. Claims 30-33, 35-38,50,52-54 and 65 ~~are~~ rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Molin et al (US Pat. 5,702,916)for reasons of record in paper number 12, paragraph 17.

14. Claims 30-33, 35-38,50,52 and 65 ~~are~~ rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Miller et al for reasons of record in paper number 12, paragraph 18.

15. Claims 30-33,35-38,48-49, 47 and 65 ~~are~~ rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Curtiss III (US Pat. 4,968,619) for reasons of record in paper number 12, paragraph 19.

16. Claims 30-33, 35-38,50,52, 53 and 65 ~~are~~ rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss (US Pat.'345) in view of Molin et al (US Pat.'916) and Hershberger et al for reasons of record in paper number 12, paragraph 20.

17. Claims 30, 33, ~~36-44,~~ 36-39,41-44, 46, 52 ~~are~~ rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss(US Pat.5,840,483) in view of Youderian (1980) for reasons of record in paper number 12, paragraph 21.

Response to Arguments

18. The rejection of claims 30-33 and 35-64 under 35 U.S.C. 112, first paragraph, (scope) is argued that "Applicants contend that the specification provides sufficient guidance that the skilled

artisan would have been able to practice the claimed methods using any bacterial cell at the time of filling" and states that working examples are shown using Salmonella and E.coli.

19. Applicants' arguments filed with respect to the functioning of Salmonella bacteriophage genes in host cells other than Salmonella have been fully considered and are partially persuasive in that Ecoli and Salmonella have been shown to function as host cells for Salmonella bacteriophage P22 genes 13 and 19, but no other host cells that would comprise the recited Salmonella bacteriophage genes have been described. There are no suggestions and teachings in the prior art to use any other host cells together with Salmonella bacteriophage late genes. No showing has been provided to show that the Salmonella bacteriophage genes would function to limit viability in any host cell other than Salmonella, and E.coli. The independent claim is not limited to Salmonella or Ecoli host cells.

20. The rejection of claims 30-33 and 35-64 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is argued that the method only requires a single step of administration.

21. Applicants' arguments filed with respect to the claims reciting an incomplete method have been fully considered but they are not persuasive because a complete method comprises a providing step, an administration step and a correlation step with the preamble of the method. The host cell need not stimulate an immune response. The cells could pass through the host and

not stimulate the immune response recited in the preamble. In order for an immune response to be stimulated to the composition, antigens contained therein must be presented to the host. Amendment of the claim to recite the essential method steps could obviate this rejection.

22. Applicant argues that claims 43, 44, 47, 51, 53-55 and 60 recite particular names of genes that are well known in the art.

23. Applicants' arguments filed with respect to claims reciting abbreviations that clearly and distinctly claim the invention have been fully considered but they are not persuasive because more than one gene can have the same abbreviation. One of the abbreviations recited is "fab". This term could refer to a gene encoding an antibody or another protein. An additional abbreviation recited is "fad" which can mean: flavin adenine dinucleotide (found in US Pat. 6228578), a DNA sequence encoding a human amyloid precursor protein called FAD (found in US Pat. 6211428) or Fanconi Anemia Genes A, B, C, D, E, F, G and H (FAA, FAB, FAC, **FAD**, FAE, FAF, FAG, FAH) found in US Pat. 6200754. Clarification of what genes the abbreviations refer to could distinctly claim Applicant's invention and obviate this rejection.

24. The rejection of claims 30-33,35-38,48-49 and 65 under 35 U.S.C. 102(b) as being anticipated by Nakayama et al (1988) **or** Curtiss et al (1989) is argued by asserting that the references:

a. Do not teach all the limitations of the claims, wherein the control mechanism that permits expression in the animal but not outside the animal and there is no control mechanism as required by the instant claims;

b.The essential gene is expressed regardless of the environment the host cell is in.

25. Applicants' arguments filed with respect to claim limitations anticipated by Nakayama or Curtiss have been fully considered but they are not persuasive.

The control mechanism of either Nakayama or Curtiss is through environmental supplementation with DAP. The independent Claim 30 does not recite specific structural controls (promoters or repressors). They are defined functionally. The essential gene would not be expressed upon depletion of DAP outside the host animal. Upon loss of the plasmid encoding the essential gene, in the absence of supplemented DAP, the host cell would not express the essential gene, resulting in cell death.

Nakayama and Curtiss both teach the essential gene does not continue to be expressed when DAP is depleted and/or the plasmid is lost outside the host animal; this control mechanism permits expression in the animal but not outside the animal. Expression of the essential gene functions as a lethal gene (claim limitations recited in section of claim 30, prior to the amendment submitted March 2001), and cell death results upon depletion of supplemented DAP. Cell death is also realized through loss of the plasmid in the absence of supplemented DAP.

Outside the animal, in the absence of DAP, essential gene function works to deplete an essential substrate, which in turn depletes a necessary metabolic component resulting in cell death.

Upon loss of the plasmid, essential gene expression would not be expressed outside the animal resulting in cell death.

With controlled supplementation of the environment inside the animal with DAP, the Asd encoding plasmid is expressed, and cell viability maintained.

The viability of host cells is limited based upon the presence or absence of the plasmid that encodes Asd which is maintained in an environment through environmental pressure controlled environmental supplementation with DAP. Without DAP in the environment, the plasmid would be lost and host cell death would result.

Applicant has not structurally defined how the asserted control is achieved in claim 30. Nakayama and Curtiss both teach species of the now claimed invention, through disclosing host cells that are environmentally limited, and do not express an essential gene upon loss of a plasmid that encodes the essential gene, and thus disclose a control mechanism that only permits viability in a permissive environment and cell death in a non-permissive environment.

26. The rejection of claims 30-33,35-38, 48-49 and 65 under 35 U.S.C. 102(e) as being anticipated by Curtiss, III (US Pat. 5,672,345) is argued:

a. To not teach all the limitations of the claims, wherein the control mechanism that permits expression in the animal but not outside the animal, nor is there a control mechanism as required by the instant claims;

b. The essential gene is expressed regardless of the environment the host cell is in.

27. Applicants' arguments filed with respect to claim limitations anticipated by Curtiss, III (US Pat. 5,672,345) have been fully considered but they are not persuasive.

Curtiss, III (US Pat. 5,672,345) teaches an essential gene environmental control system that permits expression of the essential Asd gene, present on a plasmid, which would be lost in the absence of DAP supplemented and present only in a controlled environment. Without supplementation of the environment with DAP, the Asd encoding plasmid would be lost, resulting in no essential gene expression. With no functional Asd gene in the host cell, the host cell native copy of the Asd gene has been inactivated, gene expression would not be expressed regardless of the environment.

The viability of host cells is limited based upon the presence or absence of the plasmid that encodes Asd which is maintained in an environment through environmental pressure through environmental supplementation with DAP. Without DAP in the environment, the plasmid would be lost and host cell death would result.

Applicant has functionally defined how the asserted control is achieved in claim 30, but no specific structural components are recited in this claim. Curtiss, III (US Pat. 5,672,345) teaches a species of the now claimed invention, through disclosing host cells that are environmentally limited, and do not express an essential gene upon depletion of substrate and/or through loss of a plasmid that encodes the essential gene. Curtiss III discloses a control mechanism that permits viability inside a host animal and cell death outside the animal in that absence of DAP supplementation.

28. The rejection of claims 30-33,35-38 and 65 under 35 U.S.C. 102(b) as being anticipated by Jagusztyn-Krynicka et al (1993) is argued:

a.to not disclose "differential expression of the Asd+ gene based on environmental factors";

b. does not teach all the limitations of the claims, wherein the control mechanism that permits expression in the animal but not outside the animal and there is no control mechanism as required by the instant claims;

c.the essential gene is expressed regardless of the environment the host cell is in.

29. Applicants' arguments filed with respect to claim limitations anticipated by Jagusztyn-Krynicka et al (1993) have been fully considered but they are not persuasive.

Applicants' independent claim does not require the host cells to differentially express based upon repressors or promoters that are temperature or nutrient controlled, but must only evidence expression in the animal and loss of expression outside the animal. How this loss of expression is achieved is defined functionally in claim 30.

Expression of the Asd+ gene based on environmental factors is achieved through the presence or absence of DAP added to the environment. The viability of host cells is limited based upon the presence or absence of the plasmid that encodes Asd being maintained through environmental pressure by supplementation with DAP. Without DAP in the environment, the plasmid would be lost and host cell death would result.

Jagusztyn-Krynicka et al (1993) teaches an essential gene environmental control system that permits expression of the essential Asd gene, present on a plasmid, which would be lost in the absence of supplemented DAP and present in a controlled environment, ie: the animal after administration of the host cell and DAP.

Without supplementation of the environment with DAP, the Asd encoding plasmid would be lost, resulting in no essential gene expression. With no functional Asd gene in the host cell, the host cell native copy of the Asd gene has been inactivated, essential gene expression would not be absent in the outside environment, resulting in cell death. Applicants' arguments focus on a specific embodiment that is not claimed based upon defined genetic structures. The claimed invention remains rejected for reasons of record.

30. The rejection of claims 30-33,35-38 and 65 under 35 U.S.C. 102(b) as being anticipated by Gentry-Weeks et al (1992) is argued to not teach that the essential gene is not expressed outside the animal and expressed inside the animal.

31. Applicants' arguments filed with respect to Gentry-Weeks have been fully considered but they are not persuasive because the essential gene is not expressed outside the animal upon loss of the plasmid. The plasmid is maintained through supplementation with DAP. The essential gene on the plasmid is expressed inside the animal when the environment is supplemented with DAP. Amendment of the claims to structurally define over the applied reference could obviate this rejection.

32. The rejection of claims 30-33,35-38 and 65 under 35 U.S.C. 102(b) as being anticipated by Schodel et al (Infection Immunity, May 1994) is argued to not teach that the essential gene is not expressed outside the animal and expressed inside the animal.

33. Applicants' arguments filed with respect to Schodel et al have been fully considered but they are not persuasive because the essential gene is not expressed outside the animal upon loss of the plasmid. Cell death results in no gene expression.

Expression control of the essential gene is achieved through supplementation of DAP, in order to maintain the plasmid encoding the essential gene in the host cell. An environment outside the animal without DAP would result in loss of the essential gene on the plasmid, the essential gene would not be expressed in a host cell without the plasmid, because the native copy of a host cell essential gene is inactivated. The inactivated gene is not expressed when outside the animal. The essential gene on the plasmid is expressed inside the animal when present in the host cell supplemented with DAP. Amendment of the claims to structurally define over the applied reference could obviate this rejection.

34. The rejection of claims 30-33,35-38 and 65 under 35 U.S.C. 102(b) as being anticipated by Cieslak et al (1993) is argued to not teach or suggest the limitation of the instant claims that the essential gene is expressed when the bacteria are inside the animal but not when the bacteria are outside the animal.

35. Applicants' arguments filed with respect to Cieslak et al (1993) have been fully considered but they are not persuasive because the essential gene is lost outside the animal in the absence of DAP, and would therefore not be expressed in the host cell outside the animal.

The host cell expresses the plasmid encoded essential gene inside the animal and upon withdrawal of DAP supplementation, the plasmid encoded essential gene is lost. The host cell native copy is not expressed through inactivation prior to transformation with a supplemented copy of the essential gene prior to administration of the host cell to an animal.

36. The rejection of claims 30-33, 35-38,50,52-54 and 65 under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Molin et al (US Pat. 5,702,916) is argued by asserting that

a."both fail to teach a critical limitation of the instant claims";

b."that the essential genes of the present invention are copies of a native gene, or are essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell; "This approach is not taught or suggested by Molin."

37. Applicant's arguments filed with respect to Curtiss in view of Molin have been fully considered but they are not persuasive because the critical limitation is expression of an essential gene inside an animal and no expression outside the animal, coupled with a gene that encodes for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell is taught by Curtiss who teaches host cell death outside the animal upon loss of the essential gene due to

removal of environmental pressure to maintain the essential gene encoding plasmid in the host cell. Molin was cited for teaching environmental gene regulators that are taught to provide yet another level of gene expression control based upon specific environmental temperatures, nutrients or metabolic products.

38. Applicant argues hok and sok genes described by Molin and contrasts the functions of these genes with the recited gene functions now claimed, and asserts that the claimed invention is directed to a native gene as the essential gene.

39. Applicant's arguments filed with respect to Molin have been fully considered but they are not persuasive because claims 30-33, 35-38,50,52-54 and 65 as amended do not recite the phrase "native gene" as argued, and Molin was not cited for teaching hok and sok genes relative to the claimed invention but for teaching temperature sensitive repressors and temperature sensitive promoters.

The examiner cited Curtiss in view of Molin as obviating the now claimed invention because it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the promoter of Curtiss with the temperature regulated promoter of Molin because Molin teaches the importance of regulated transcription associated with cell killing function, and a successful means of accomplishing this regulatory function is through change of temperature that would result in the control of expression of essential or lethal genes.

40. The rejection of claims 30-33, 35-38,50,52 and 65 under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Miller et al is argued:

a.through referring to the arguments for Curtiss under 35 U.S.C. 102;

b.asserting that Miller does not define:

i. a biological containment system; and

ii.for limiting the expression of the heterologous antigen in a non-permissive environment.

c.that neither Miller nor Curtiss suggest the use of the promoter of Miller in the system of Curtiss

d.and "The critical limitation of the instant claims, that the essential gene is expressed in a permissive environment but not in a non-permissive environment is simply not taught by any of the cited references."

41. Applicant's arguments filed with respect to Curtiss in view of Miller have been fully considered but they are not persuasive because

a. in the absence of DAP, host cell expression of Asd encoded by the plasmid inserted into the cell would not be able to maintain cell viability, the plasmid would be lost resulting in cell death.

b. Inside an animal supplemented by DAP, a permissive environment is defined and in the absence of DAP outside the animal a non-permissive environment results. The essential gene is expressed in a permissive environment and not expressed in a non-permissive environment.

c.Curtiss does teach the importance of using a promoter for gene expression. Miller was cited to show the utilization of promoters that promote selective gene expression. Curtiss is directed to environmental control and expression of an essential gene. Control of essential gene expression is clearly taught through limiting host cell essential gene expression through dependence upon environmental conditioning through addition of DAP. Genetic expression based upon environmental factors is taught by Curtiss. Miller teaches another type of environmental control, based upon temperature or iron.

d. With respect to Applicant's assertion that there is no suggestion to combine the teachings of Miller ('901) with Curtiss, it is the position of the examiner that Curtiss is interested in environmentally controlling genetically ~~engineer~~ engineered host cells and Miller teaches the importance of regulated gene expression through using a temperature sensitive promoter that provides the advantage of increased environmental control of engineered host cells.

e. Applicant's arguments do not comply with 37 CFR 1.111© because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

42. The rejection of claims 30-33,35-38,48-49, 47 and 65 under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Curtiss III (US Pat. 4,968,619) is argued:

a.to not teach "an environmentally controlled promoter linked to the essential gene";

b.asserts that the essential gene is expressed regardless of the environment that the host cell is in; and

c.there is no motivation to use such regulation because the function of those systems would not be improved by regulation of the essential gene.

43. Applicant's arguments filed with respect to either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Curtiss III (US Pat. 4,968,619) have been fully considered but they are not persuasive because ;

a. the claimed invention of claim 30 is not limited to an environmentally controlled promoter linked to the essential gene. Applicant's argument is not commensurate in scope with the claimed invention;

b.the essential gene would not be expressed regardless of the environment the host cell is in, rather the essential gene would be lost in a non-permissive environment and/or would deplete essential substrate for viability, resulting in cell death and non-expression of the essential gene.

c. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Curtiss ('619) teaches the combination of polA regulation together with an essential gene mutation results in a vast improvement in safety over that afforded by only using a single essential gene mutation alone; the reference suggests the use of delta-Asd mutant and delta-thymidine mutants that are regulated.

Curtiss ('619) also teaches that through the use of an environmentally responsive promoter, the expression genes do not express the heterologous protein at times when such expression would be undesirable, specifically during culture, vaccine preparation, or storage, contributing to the viability of the cells, but when administered to humans or animals, express large amounts of the protein. This is desirable because high expression of many heterologous proteins in Salmonella can be associated with toxicity to the bacterium. The use of only a single integrated copy of the DNA encoding the heterologous protein also contributes to minimal expression of the heterologous expression antigen at times when expression is not desired.

44. The rejection of claims 30-33, 35-38,50,52, 53 and 65 under 35 U.S.C. 103(a) as being unpatentable over Curtiss (US Pat.'345) in-view of Molin et al (US Pat.'916) and Hershberger et al is argued:

through asserting that the systems of Curtiss and Hershberger have no utility in biological containment of a host cell

45. It is the position of the examiner that Curtiss clearly teaches a host cell that is attenuated and maintained through environmental supplementation with DAP. Without supplementation with DAP, the host cell would die outside the host animal. The host cells of Curtiss have utility in biologically limiting host cell viability through environmental pressures to effect viability of genetically engineered host cells.

With respect to Hershberger, the reference was applied to the claims because Hershberger provides the art of recombinant host cells an improved selective system that solves the problem of stabilizing and selecting recombinant DNA containing host cells while concurrently maximizing gene expression and biosynthesis of a functional expression antigen (polypeptide).

46. Applicant further asserts that the host cells comprise a copy of a native gene or a gene essential for metabolism, growth, cell wall integrity or cell membrane integrity, wherein the essential gene is expressed in a premissive environment and not expressed in a non-permissive environment and concludes "[N]one of the cited references teaches this limitation".

47. Contrary to Applicant's assertion, the host cell of Curtiss, III is environmentally limited based upon retention of the essential gene encoding plasmid which is contingent upon supplementation of the environment with DAP. Inside the animal DAP is provided, providing for host cell stability, viability and expression of the essential gene inside the animal (a permissive

environment), while in a non-permissive environment outside the animal, DAP is not provided resulting in host cell death, due to loss of the functional essential gene encoding plasmid.

48. It is argued that Hershberger and Curtiss, III would not benefit from controlled expression of the gene because the gene is expressed under all environmental conditions.

49. Contrary to Applicant's assertion that the gene is expressed under all environmental conditions, it is the position of the examiner, that in the absence of DAP the host cell would become unstable and lose the essential gene encoding plasmid resulting in non-expression of the essential gene in such an environment. Therefore, the gene is not expressed in all environments as argued.

50. Applicant asserts that Molin does not to teach regulation of an essential gene that is a copy of the native gene. Applicant points to the sok gene as being the only gene under an environmental regulation expression mechanism and is a non-native gene.

51. It is the position of the examiner that is assertion is not commensurate in scope with the claimed invention recited in claims 30-33, 35-38,50,52, 53 and 65. The claim limitation argued is recited in claims withdrawn from consideration, election by original presentation.

52. The combination of the cited references is asserted not to provide any benefit through regulation of a system designed to retain a vector in a host cell population.

53. It is the position of the examiner that regulation of a system that expresses an expression antigen, as well as a plasmid that encodes an essential gene provides the benefit controlling expression antigen expression level in the appropriate environment to effect stimulation of an immune response at the appropriate time, as well as to define a safe genetically engineered host cell that is not introduced into the outside environment, but is viability limited in view of controlled essential gene expression.

54. The asserted arguments are summarized through stating that there is no suggestion or motivation to combine the teaching of the applied references, nor has a prima facie case of obviousness been established.

55. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the references teach and suggest means and methods for the successful and effective environmental control of recombinantly produced host cells, wherein regulation of

expression of an essential gene, and an antigen expression gene are stabilized, maximized and expressed inside the animal and not stabilized outside the animal, resulting in non-expression of the essential gene. The host cell produced contains a viability limiting system through genetic means which affords control of cell viability effected by environmental factors and which provides for increased environmental safety due to loss of host cell viability when the cell enters the outside environment..

56. The rejection of claims 30,33, 36-44, 46, 52 under 35 U.S.C. 103(a) as being unpatentable over Curtiss(US Pat.5,840,483) in view of Youderian (1980) is argued that there is no environmental control mechanism associated with the Asd gene.

57. It is the position of the examiner that environmental control was used by Curtiss through supplementation of DAP to the environment in order to control host cell viability and growth inside the animal to which it was administered.

58. Applicant asserts that there is no benefit from a control mechanism taught by the applied references.

59. Contrary to Applicant's assertion that there are no benefits realized, it is the position of the examiner that the host cell with a control mechanism provides the benefit of directed expression of bacterial antigens based upon environmental factors.

60. Applicant further asserts that x3115 does not comprise a control mechanism as required by the instant claims.

61. Contrary to Applicant's assertion,strain x3115 does meet the limitations of the now claimed invention, wherein the strain comprises P22, a lethal gene that can function to kill a host cell through lysis, as well as comprises an essential gene Asd for administration to a warm blooded animal. What specific control mechanism Applicant asserts is required, not specifically recited in the claims. Applicant's arguments are not commensurate in scope with the claimed invention that need only evidence any type of control that limits viability in a non-permissive environment.

62. Applicant further asserts that the examiner's statement is false and argues "Thus, the extrachromosomal vector carrying the Asd gene is stabilized in the population of host cells because without that vector, the product of the Asd gene, which is essential to cell viability, is absent.

63. It is the position of the examiner that through supplementation of the environment inside the animal with DAP, the extrachromosomal vector carrying the Asd gene is stabilized in the population of host cells. The cells remain viable through the supplementation of DAP, which would other wise be lost and viability negatively effected.

64. Applicant asserts that all the elements of the claimed invention are not be met.

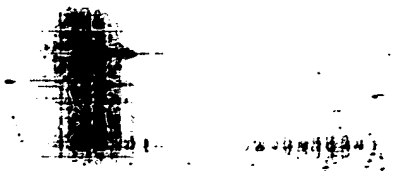
65. In response to Applicant's assertion, it is the position of the examiner that Curtiss in view of Youderian et al provide the person of ordinary skill in the art at the time the invention was made

with guidance and teaching with respect to use of a Salmonella strain of Curtiss, X3115 that comprised P22, would encode both gene 19 and gene 13 of P22 that would provide for environmental control of the host cell to afford antigen expression in a permissive environment (inside an animal host) and cell death through lysogenic products from gene 19 and gene 13 of bacteriophage P22, in a non-permissive environment (outside an animal host) . No showing of unexpected results has been provided, nor have non-obvious structural components been recited in the claims. The applied references obviate the now claimed invention.

Conclusion

66. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.



67. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

May 21, 2001

L. F. Smith

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